

USSN 09/636,243  
8325-1004  
M4-US1



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In Re Application of:	)	Examiner: T. Wessendorf
	)	
WANG and PABO	)	Group Art Unit: 1639
	)	
For: <b>DIMERIZING PEPTIDES</b>	)	Confirmation No.: 6438
	)	
Serial No.: 09/636,243	)	
	)	
Filed: August 10, 2000	)	
	)	
Atty. Docket No.: 8325-1004 (M4-US1)	)	
	)	
	)	

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**SUPPLEMENTAL BRIEF ON APPEAL  
PURSUANT TO 37 C.F.R. §1.193(b)(2)(ii)**

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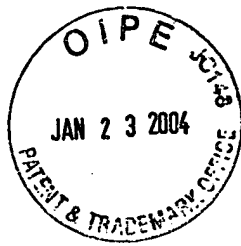
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Michelle Hobson  
Signature

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**SUPPLEMENTAL BRIEF ON APPEAL**

Mail Stop Appeal Brief  
Commissioner for Patents  
Alexandria, VA 22313

Sir:

**INTRODUCTION**

Appellants submit in triplicate their supplemental brief on appeal in accordance with 37 C.F.R. §1.193(b)(2)(ii). A Notice of Appeal was filed July 8, 2003 and a Brief on Appeal was filed on August 5, 2003. Prosecution on the merits was reopened in an Office Action mailed on October 20, 2003 and all claims were non-finally rejected under 35 U.S.C. § 112, first and second paragraphs, as well as under 35 U.S.C. §§ 102 and 103. The specification was also objected to as allegedly confusing and containing new drawings. Pursuant to 37 C.F.R. § 1.193(b)(2)(ii) and submission of this Supplemental Brief on Appeal, Appellants request reinstatement of the appeal.

### **I. REAL PARTIES IN INTEREST**

The statement regarding the parties of interest filed in the Brief on Appeal submitted August 5, 2003 remains applicable and is hereby incorporated by reference.

### **II. RELATED APPEALS AND INTERFERENCES**

The statement regarding related appeals and interferences filed in the Brief on Appeal submitted August 5, 2003 remains applicable and is hereby incorporated by reference.

### **III. STATUS OF THE CLAIMS**

Claims 5, 6 and 20 are currently pending in the above-referenced case (hereinafter "the application"). Claims 1-4 and 7-19 have been withdrawn from consideration pursuant to a Restriction Requirement mailed on July 25, 2002; traversed by Appellants on August 26, 2002 and made FINAL in an Office Action mailed on September 25, 2002.

The application was originally filed on August 10, 2000 with claims 1 to 19. A substitute specification and preliminary amendment were filed on January 30, 2001. The Office approved the substitute specification and, subsequent to approval, a Restriction Requirement was mailed on July 25, 2002. In a Response to Restriction Requirement, dated August 26, 2002, claims 5 and 6 were elected with traverse. In an amendment filed on December 19, 2002, claims 5 and 6 were amended and claim 20 was added. A Notice of Appeal was filed July 8, 2003 and a Brief on Appeal was filed on August 5, 2003. Prosecution on the merits was reopened in an Office Action mailed on October 20, 2003. Pursuant to 37 C.F.R. § 1.193(b)(2)(ii) and submission of this Supplemental Brief on Appeal, Appellants request reinstatement of the appeal.

All pending claims remain rejected under 35 U.S.C. § 112, first and second paragraphs and under 35 U.S.C. § 102. New grounds of rejection of claims 5, 6, and 20, based on 35 U.S.C. § 102 and § 103 were set forth in the Office Action mailed on October 20, 2003 reopening prosecution after appeal. Thus, claims 5, 6 and 20 are pending as shown in Appendix A.

#### **IV. STATUS OF THE AMENDMENTS**

The status of the amendments filed in the Brief on Appeal submitted August 5, 2003 are applicable and are hereby incorporated by reference. Pursuant to 37 C.F.R. § 1.193(b)(2)(ii), no new amendments are made herein.

#### **V. SUMMARY OF THE CLAIMS**

The summary of the claims filed in the Brief on Appeal submitted August 5, 2003 is applicable and is hereby incorporated by reference.

#### **VI. ISSUES ON APPEAL**

1. Whether the drawings as described in the substitute specification were contained in the originally filed specification.
2. Whether the headings in the substitute specification are unduly confusing.
3. Whether the specification provides adequate written description for pending claims 5, 6 and 20 under 35 U.S.C. § 112, first paragraph.
4. Whether pending claims 5, 6 and 20 are sufficiently definite under 35 U.S.C. § 112, second paragraph.
5. Whether pending claims 5 and 6 are anticipated by Kim et al. (1998) *Proc. Nat'l Acad. Sci. USA* 95:2812-2817 under 35 U.S.C. § 102(b).
6. Whether pending claims 5 and 20 are anticipated by Pomerantz et al. (1998) *Biochemistry* 37(4):965-970 under 35 U.S.C. § 102(b).

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7. Whether pending claims 5, 6 and 20 are obvious over Kim et al. (1998) *Proc. Nat'l Acad. Sci. USA* 95:2812-2817 under 35 U.S.C. § 103(a).

Appellants note that Issues (1) through (4) set forth above are unchanged and were all addressed in the Brief on Appeal filed on August 5, 2003.

Issue (5) as set forth above differs from Issue (5) as addressed in the Brief on Appeal inasmuch as claim 6 is newly rejected as allegedly anticipated by the same reference previously applied only to claim 5.

Issue (6) as addressed in the Brief on Appeal filed August 5, 2003 (namely, the rejection of claims 5, 6 and 20 over Paveltich et al) has been withdrawn. Thus, issues (6) and (7) as set forth above are newly raised by the Examiner.

## **VII. GROUPING OF CLAIMS**

Appellants herein incorporate by reference the statements made in the Brief on Appeal filed August 5, 2003 regarding the Grouping of the Claims.

## **VIII. ARGUMENTS**

### **1. No drawings were added in the Substitute Specification**

Appellants herein incorporate by reference the arguments made in the Brief on Appeal filed August 5, 2003 regarding the drawings (Issue 1).

### **2. The Headings in the Specification are not confusing**

Appellants herein incorporate by reference the arguments made in the Brief on Appeal filed August 5, 2003 regarding the headings in the specification (Issue 2).

### **3. The Specification Describes the Claims on Appeal**

Appellants herein incorporate by reference the arguments and diagrams made in the Brief on Appeal filed August 5, 2003 regarding 35 U.S.C. § 112, first paragraph, written description (Issue 3).

### **4. Claim 5 is definite**

Appellants herein incorporate by reference the arguments made in the Brief on Appeal filed August 5, 2003 regarding 35 U.S.C. § 112, second paragraph (Issue 4).

### **5. Anticipation by Kim et al. has not been established**

Appellants herein incorporate by reference the arguments made in the Brief on Appeal filed August 5, 2003 regarding the rejection of claim 5 over Kim under 35 U.S.C. § 102(b) (Issue 5 in Brief on Appeal and above).

With respect to the newly raised rejection of claim 6 as allegedly anticipated by Kim, the Office action states: "Claim 6 would be inherent to Kim's disclosure of describing the specific linkers at Fig. 2 and disclosure that these sequences can be attached to the N and C terminus of Zif 268." (Office action of October 20, page 12)

Appellants note that claim 6 contains all of the limitations of claim 5, which include:

1. a complex comprising two or more fusion proteins
2. each fusion protein comprises a zinc finger protein and a peptide linker
3. the peptide linkers are non-naturally-occurring peptides
4. the fusion proteins are joined to each other by binding of the peptide linkers.

Claim 6 additionally recites that the peptide linker of each fusion protein is the same (*i.e.*, has the same amino acid sequence).

Kim fails to disclose or suggest the binding of two or more fusion proteins to each other wherein the binding is mediated by non-naturally-occurring peptide linkers, as claimed. *See*, for example the specification at page 10, lines 22-29. Both of the examples cited in the Office Action (the 268/NRE and 268//NRE constructs) are single, covalently continuous proteins. Neither is a complex of two or more proteins wherein the two or more proteins are joined to each other by non-naturally-occurring peptide linkers. *See* Figure 2A of Kim.

Careful reading of Kim indicates that his use of the term “linker” refers to the amino acid sequence located between two zinc fingers of a single multi-finger protein. *See, e.g.*, Kim Figure 2A, in which his longer linkers<sup>1</sup> are shown to be covalently continuous with the sequences of the flanking zinc fingers<sup>2</sup>; and Kim at page 2812, first column, wherein it is stated: ‘... previous design strategies for poly-finger proteins – which all used canonical “TGEKP” linkers to connect the additional fingers ...’ (emphasis added). By contrast, the claimed linkers are specified in the claims to be non-naturally occurring peptide sequences which mediate dimerization of two or more proteins.

Moreover, numerous portions of Kim’s paper attest to the fact that the 268/NRE and 268//NRE constructs disclosed therein are single proteins; nowhere does Kim disclose or suggest any type of peptide sequences capable of mediating the formation of a complex of two or more proteins. *See*, for example, page 2812, second column, lines 7-8 (“Here, we report the design and characterization of six-finger peptides ...”); page 2814, second column, lines 2-3

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<sup>1</sup> Having the amino acid sequences RQKDGERP and RQKDGGGSERP

<sup>2</sup> Indicated in the figure by boxed and wavy underlined amino acid sequences



("Equilibrium titrations show that the 268//NRE peptide has significantly higher affinity for the composite sites . . .", emphasis added); page 2814, second column, lines 47-48 ("We also used competition experiments to further study the affinity and specificity of the six-finger 268//NRE peptide." emphasis added); page 2816, second column, second paragraph of "Discussion" section ("Simple arguments from physical chemistry suggest that dramatic increases in DNA-binding affinity might be obtained using the "chelate effect" and covalently linking two three-finger peptides." emphasis added); page 2817, first column, first full paragraph ("Our new six-finger peptides . . .") and page 2817, second column, lines 18-19 (Can covalently-linked proteins – such as these new poly-finger proteins – achieve a level of specificity . . . ?" emphasis added). Additional examples abound in Kim's manuscript.

Simply put, Kim does not disclose linking two or more proteins via a peptide linker on each protein, as claimed. Accordingly, this reference cannot anticipate claims 5 or 6.

#### **6. Anticipation by Pomerantz et al. has not been established**

In the Office Action mailed on October 20, 2003, the Examiner reopened prosecution on the merits "in view of the newly cited art." (Office Action, page 2). In addition to the new rejection of claim 6 under §102(b), discussed above, claims 5 and 20 were newly rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Pomerantz (Biochemistry). (Issue 6, above). On page 12 of the Office Action, Pomerantz was cited for allegedly disclosing:

a zinc finger complex comprising the same zinc fingers 1 and 2 from ZIF268 with a dimerizing peptide and linker from GAL4 that forms a dimer with a target. See page 966, Materials and Methods and RESULTS starting at page 967.

With regard to this new rejection, The Examiner identifies the reference simply as "Pomerantz (Biochemistry)." The Office provided neither a full citation, nor a copy of the cited reference. Applicants request clarification and complete citation of the reference from the Examiner but will assume, for the purposes of this Brief, that the newly-cited reference is that disclosed as reference AP-1 in Applicants' Information Disclosure Statement mailed July 6, 2001.

If this assumption is correct, Applicants note that this newly applied reference was received in the PTO on July 9, 2001 and was reviewed by the present Examiner on September 19, 2002. (Copy of initialed page from PTO-1449 attached). Between the time that the Examiner reviewed the Pomerantz reference and the filing of Applicants' Appeal Brief, two Office Actions were issued (Sept. 25, 2002 and April 8, 2003), neither of which cited the Pomerantz reference. In the present Office Action (the third since the Examiner reviewed the Pomerantz reference) no reason is given as to why this reference was not cited earlier in the prosecution.

Notwithstanding this curious delay, Appellants note that there is nothing in the Pomerantz reference that describes, demonstrates or suggests the claimed subject matter. The claims on appeal clearly require linking of two or more proteins via non-naturally occurring peptides. In contrast, the dimerizing linker used by Pomerantz, namely amino acids 41 to 100 of GAL4, is clearly a naturally-occurring peptide sequence, inasmuch as it is part of the naturally-occurring GAL4 protein

Because Pomerantz does not describe or demonstrate the elements of the claims on appeal, this reference does not anticipate these claims. Moreover, the fact that Pomerantz successfully used naturally-occurring sequences as dimerization domains provides no motivation to explore the use of non-naturally-occurring peptides as dimerizing linkers.

**7. Claims 5, 6 and 20 are not obvious in view of Kim et al.**

In the Office Action mailed on October 20, 2003, the Examiner also newly rejected claims 5, 6 and 20 under 35 U.S.C. § 103(a) as allegedly obvious in view of Kim (above), stating:

Kim does not explicitly recites that each zinc finger contains a linker, as claimed. However, Kim discloses each zinc finger contains at the N and C terminus a linker. This would, at least, suggests that, each finger proteins has its own linker(s). It is these linkers attached at the terminal ends of the embedded that obviously bind with each another rather, than the embedded zinc fingers. (Office Action, page 13).

Appellants do not understand the rejection as set forth by the Examiner.

Furthermore, as with Issue 6, addressed above, Appellants find it curious that the Examiner would, at this late date, introduce a rejection pursuant to 35 U.S.C. § 103(a) based on a reference that has been repeatedly applied (and addressed) under 35 U.S.C. § 102(b).

In any event, for the reasons noted in the Brief on Appeal filed August 5, 2003 and reiterated herein, Kim does not suggest the compositions as set forth in claims 5, 6 and 20.

The pending claims all contain, at least, the following elements:

1. a complex comprising two or more fusion proteins
2. each fusion protein comprises a zinc finger protein and a peptide linker
3. the peptide linkers are non-naturally-occurring peptides
4. the fusion proteins are joined to each other by binding of the peptide linkers.

Kim fails to suggest these elements. Rather, Kim describes several single proteins (as discussed above in the arguments relating to Issue 5). Kim does not in any way teach or suggest complexes of two or more fusion proteins joined by linkers; in which each fusion protein contains a zinc finger protein and a non-naturally-occurring peptide linker. *See*, for example the specification at page 10, lines 22-29. Moreover, Kim's ability to covalently link two three-finger proteins, to form a single six-finger protein, provides no motivation to explore the use of dimerizing peptides to link zinc finger proteins, as claimed.

In fact, contrary to the Office's assertions, Kim's teachings regarding covalent linkage of zinc fingers is utterly irrelevant to the pending claims. As noted above, Appellants use the term "linker" to refer to peptides that mediate dimerization between two or more separate and distinct proteins. In contrast, Kim uses the term "linker" to refer to a peptide sequence that covalently joins one zinc finger to another within a single protein. Dimerization between two proteins, on the one hand, and covalent linkage of sequences within a single protein, on the other, are entirely different concepts. Consequently, there is nothing disclosed by Kim that would direct one working in this field toward the claimed subject matter.

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Because there are no teachings or suggestions in Kim which would lead a skilled artisan to use non-naturally-occurring dimerizing peptides to link zinc finger-containing fusion proteins, the subject matter as claimed is not obvious in view of Kim.

#### **8. Additional Arguments Regarding Separately Grouped Claims**

Appellants herein incorporate by reference the additional arguments made in the Brief on Appeal filed August 5, 2003 regarding separately grouped claims (Issue 6 in the August 5, 2003 Brief).

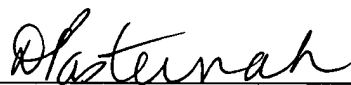
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**CONCLUSION**

For the reasons stated above, Appellants respectfully submit that the pending claims are patentable over the art cited by the Examiner and, in addition, are described and sufficiently definite. Appellants also submit that all drawings were present in the originally-filed application, and that the specification conforms to PTO requirements. Accordingly, Appellants request that the objections to the specification and the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: January 20, 2004

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### CLAIMS ON APPEAL

5. (previously presented): A zinc finger complex, comprising two or more fusion proteins, each fusion protein comprising a zinc finger protein and a peptide linker, wherein the fusion proteins are joined to each other by specific binding of the peptide linkers, and wherein the peptide linkers are non-naturally occurring peptides.

6. (previously presented): The zinc finger complex of claim 5, wherein the peptide linker of each fusion protein is the same.

20. (previously presented): The zinc finger complex of claim 5, wherein the zinc finger protein of each fusion protein has the same sequence.